New claim 23-28 have been added. Support for the new claims is found, for example, at page 6, lines 9-18; and page 9, line 26 to page 10, line 15. A copy of the claims as amended is attached in an Appendix for the convenience of the Examiner.

I. Information Disclosure Statement

A Supplemental Information Disclosure Statement is attached to this Amendment, along with one page of Form PTO-1449 and copies of the references cited therein. This IDS cites four English-language patent documents that are equivalent to the four foreign patent documents cited in the Information Disclosure Statement mailed November 18, 1999, which the Examiner did not consider. Applicants respectfully request consideration of these publications and return of the initialed Form PTO-1449.

II. Objection to Claims

Claim 16 was objected to for allegedly failing to further limit claim 15. Applicant respectfully traverses the objection if applied to the amended claims.

Claim 15 is directed to a method for making the drug composition, wherein a weakly acidic drug is first converted into an alkali metal salt. The alkali metal salt then is coated onto the inner core once the conversion (in the first step) has taken place. In contrast, claim 16 requires that in the method of claim 15 the alkali metal salt be formed **as part of** the coating process, as for example described at page 6, line 20 to page 7, line 4. Claim 15 does not require that the salt be formed as part of the coating process. Therefore, it clearly would be possible to infringe claim 15 and not claim 16, simply by eliminating the process of forming the salt as part

of the coating process (see new claim 23). Nonetheless, claim 16 has been amended to make this distinction more clear.

III. Rejections under 35 U.S.C. § 103

Claims 1-14 and 21-22 were rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,376,384 to Eichel et al. ("Eichel") in view of U.S. Patent No. 5,180,832 to Freyne et al. ("Freyne"). Claims 15-17 and 19 also were rejected under 35 U.S.C. §103(a) as obvious over Eichel in view of Freyne. Applicant respectfully traverses the rejections if applied to the amended claims.

Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992).

Applicants' Claimed Compositions and Methods

Applicant has developed improved compositions for the controlled delivery of drug to the colon. The claimed composition includes pellets having (1) an **inner core including a drug**; and (2) a **rate-controlling membrane coating** the inner core. The claimed composition further requires (3) a **means to prevent release of the drug until the composition reaches the terminal ileum or colon** following oral administration of the composition. This means to prevent release is described in detail at page 8, line 16 to page 11, line 22.

Eichel

Eichel discloses a drug delivery composition with a coating comprising a controlled release polymer, such as ethyl cellulose or acrylic resin, and an additive that is incorporated into the coating. It is the additive that controls the rate of hydration and permeability of the coating (see col. 4, lines17-22). **These compositions are not remotely adapted to prevent release until the composition reaches the terminal ileum or colon.**

Furthermore, there is no suggestion in Eichel of using the composition to provide delivery of an alkali metal salt of a weak **acid**, as the preferred drugs disclosed in Eichel are all weakly *basic*.

Freyne

Freyne discloses drug compositions of [[[(3-pyridinyl)methylen]amino]oxy]alkanoic acids and esters (abstract). The compounds can be converted to their therapeutically active non-toxic metal or amine substitution salt forms (col. 5, lines 58-62). Freyne, however, does not remotely disclose or suggest incorporating such salts into a *solid, controlled release form*, particularly one for colonic delivery. In fact, the only benefit Freyne discloses for the salt forms is that their "increased water solubility over the corresponding base form are obviously more suitable in the preparation of **aqueous** compositions" (col. 7, lines 37-40) (emphasis added).

Moreover, contrary to the Examiner's allegation, nothing in Freyne discloses a *controlled* release dosage form. The portions of Freyne cited by the Examiner merely highlight the myriad

of immediate or delayed release dosage forms disclosed. For instance, Example 32 in Freyne appears to disclose an immediate release, not a controlled release, unit dosage form.

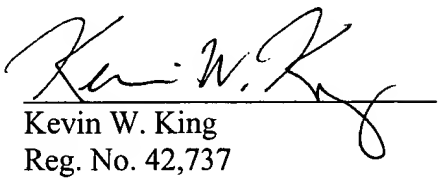
Eichel in Combination with Freyne

One of ordinary skill in the art would not be motivated to combine Eichel with Freyne, since there is no suggestion to do so, absent hindsight of the present application. Nonetheless, even if combined, Eichel and Freyne clearly fail to provide the motivation for one of ordinary skill in the art to modify the formulations of either Eichel or Freyne to derive applicants' claimed compositions which provide sustained delivery of a drug within the colon by incorporating a slow-release drug pellet into a colon-targeted dosage form. The Examiner has identified nothing in the prior art that suggests combining a drug having the defined properties into a composition form adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration. Thus, no *prima facie* case of obviousness has been established. Applicant therefore is not required to set forth objective evidence of nonobviousness.

The claims as amended are thus novel and nonobvious over the prior art of record.

Allowance of claims 1-14 and 21-28 is therefore earnestly solicited.

Respectfully submitted,



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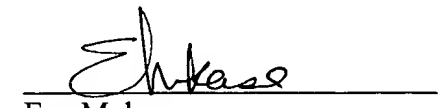

Eva Mukasa

Date: May 22, 2000

Appendix

Claims as Amended

1. (Once amended) A controlled release composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. (Once amended) The composition of claim 1 wherein the drug is a thromboxane synthase A_2 inhibitor or a thromboxane A_2/prostaglandin endoperoxide receptor antagonist.

3. (Once amended) The composition of claim 2 wherein the drug is ridogrel.

4. (Once amended) The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. (Once amended) The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. (Once amended) The composition of claim 5 wherein the rate-controlling membrane is formulated from EUDRAGIT™ NE30D.

7. (Once amended) The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. (Once amended) The composition of claim 1 wherein the inner core is a sugar sphere.

9. (Once amended) The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. (Amended) The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. (Once amended) The composition of claim 1 wherein the salt is an alkali metal salt.

12. (Once amended) The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. (Once amended) The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. (Once amended) The composition of claim 1 wherein the drug is used for a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. (Once amended) A method for making a composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising

making a salt of the drug, and

coating the salt onto the inner cores.

16. (Twice amended) The method of claim 15 wherein the salt is [prepared as part of a preparation process for] <u>made in a solution used in</u> the coating of the inner cores.

17. (Once amended) A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, the method comprising

administering the drug in a composition comprising pellets,

wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

18. (Cancelled).

19. (Once amended) A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, the method comprising

administering to a patient in need of treatment a composition comprising pellets,

wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

20. (Cancelled).

21. The composition of claim 1 wherein the pellets are compressed into tablets which are coated to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.

23. (New) The method of claim 15 wherein the salt, after being made, is recovered in solid form before coating onto the inner cores.

24. (New) The composition of claim 1 wherein the pellets are administered in a capsule coated with a mixture of a first copolymer of methacrylic acid and methylmethacrylate and a second copolymer of methacrylic acid and methylmethacrylate, which disintegrate and release the pellets in the terminal ileum or in the colon following oral administration.

25. (New) The composition of claim 24 wherein the first copolymer dissolves at pH 6 or greater and comprises about 48% methacrylic acid units per gram dry weight of first copolymer and wherein the second copolymer dissolves at pH 7 or greater and comprises about 29% methacrylic acid units per gram dry weight of second copolymer.

26. (New) The composition of claim 25 wherein the ratio of first polymer to second polymer in the mixture is between 100:0 and 20:80.

27. (New) The composition of claim 25 wherein the capsule coating has a thickness between about 150 and 200 μm.

28. (New) The composition of claim 25 wherein the capsule coating has a thickness between about 80 and 120 μm.